REMARKS

In this communication, Applicants have amended Claims 1-3, 16 and 21-23; canceled Claims 5-13, and 20; and added new Claims 24-33. No new matter is introduced. Claims 1-4, 14-19, and 21-33 are pending. Allowance of all pending claims is respectfully requested.

Rejections under 35 U.S.C. § 112

Claims 1-23 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for reasons stated on page 2 of the Office Action. Claims 1-3, 16, 21 and 22 have been amended to address the Examiner's concerns. In response to the Examiner's question on why two steps of disulfide bond reduction are recited in the method, Applicants have amended the claim to recite a deprotecting step to remove the blocking reagent and thus generate free thiol groups for reacting with the tagging reagent (page 11, lines 8-9).

Claims 16-19 and 21-23 stand rejected under 35 U.S.C. § 112, first paragraph, as being not enabling for reasons stated on page 3 of the Office Action. Specifically, the Examiner alleges that the specification does not reasonably provide enablement for all possible compounds having a thiol-specific reactive group attached to a non-biological polymer via a linker. Applicants respectfully traverse the rejection.

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. MPEP, 2164.01. The standard for determining whether the specification meets the enablement requirement is whether the experimentation needed to practice the invention undue or unreasonable. Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916). Accordingly, even though the statute does not use the

term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant invention is directed to compositions and methods to tag cysteine-containing peptides for high-throughput quantitative protein analysis. Claims 16-19 and 21-23 encompass compounds having a thiol-specific reactive group linked to a non-biological polymer. Thiol-reactive functional groups are well-known in the art. For example, Molecular Probes Inc., a company specialized in peptide detection, teaches at its website that commonly used thiol-specific reactive groups include alkylating reagents, such as iodoacetamides, maleimides, benzylic halides and bromomethylketones, arylating reagents, such as NBD halides, and many of the amine-reactive reagents, such as isothiocyanates and succinimidyl esters (see" Introduction to Thiol Modification and Detection" at Molecular Probes Inc.'s website). The non-biological polymers have been clearly defined on page 4 of the specification.

The level of one of ordinary skill in the art is high in the field of biotechnology.

Typically, a person practicing the instant invention would have a Ph.D. degree in biochemistry or a related field, and have one or more years of post-doctorate experience in protein chemistry. The reaction between a free thiol group and any thiol-specific reactive group is highly predictable in the chemical/biochemical art. Moreover, Applicants have provided a working example to demonstrate how to synthesize a non-biological polymer and how to link the polymer to a thiol-specific reactive group. Considering the fact that the raw materials for synthesizing the compound of the present invention are easily identifiable by one skilled in the art, and the fact that the synthesis procedure involves only routine, predictable chemical reactions, Applicants respectfully submit that the instant invention can be practiced by one of ordinary skill in the art without undue experimentation. Accordingly, Claims 16-19 and 21-23 are fully enabled by the specification. Withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 102

Claim 16 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Huang et al. (hereinafter "Huang") for reasons stated on page 4 of the Office Action. Applicants respectfully traverse the rejection.

For anticipation under 35 U.S.C. § 102, the reference "must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present." MPEP § 706.02, distinction between 35 U.S.C. § 102 and § 103, page 700-21.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Claim 16, as amended, is directed to a compound useful for capturing cysteine-containing peptides. The compound comprises a thiol-specific reactive group attached to a non-biological polymer via a linker. The thiol-specific reactive group **forms a non-disulfide, covalent bond** with a thiol group on a cysteine-containing peptide.

Huang generally describes methods for preparing polyethylene glycol (PEG) copolymers for carrying and releasing cycteine-containing peptides. The PEG copolymers of Huang contain a cysteamine-thiopyridine group that **forms a disulfide bond** with the cysteine-containing peptides. In fact, the PEG copolymers of Huang are not capable of forming **a non-disulfide, covalent bond** with a thiol group on the cysteine-containing peptides. Therefore, Huang does not teach every element of Claim 16. Accordingly, Applicants respectfully submit that Claim 16 is not anticipated by Huang. Withdrawal of the 35 U.S.C. § 102(b) rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1-4, 14-19 and 21-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Aebersold et al (WO 00/11208, hereinafter "Aebersold") in view of Huang for reasons stated on pages 5-6 of the Office Action. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

In addition, when applying 35 U.S.C. § 103, the following tenets of patent law must

be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Independent Claim 1 is directed to a method for the analysis of mixtures containing proteins. The method comprises the steps of: (a) reducing disulfide bonds in the proteins of a sample, thereby generating free thiol groups in cysteine-containing proteins; (b) blocking the free thiol groups with a blocking reagent; (c) digesting the proteins in the sample to generate cysteine-containing peptides; (d) deprotecting the peptides to remove the blocking reagent, thereby providing thiol groups in cysteine-containing peptides for reaction; (e) reacting the cysteine-containing peptides in the sample with a tagging reagent, wherein said tagging reagent comprises a thiol-specific reactive group which is attached to a polymer tag via a linker, wherein the linker can be differentially labeled with stable isotopes and wherein the polymer tag forms a covalent bond with the cysteine-containing peptides; (f) washing the polymer tag to remove non-covalently bound peptides; (g) eluting the cysteine-containing peptides from the polymer tag; and (h) subjecting the eluted peptides to quantitative mass spectrometry (MS) analysis.

Independent Claim 16, as amended, is directed to a compound useful for capturing cysteine-containing peptides. The compound comprises a thiol-specific reactive group attached to a non-biological polymer via a linker. The thiol-specific reactive group forms a non-disulfide, covalent bond with a thiol group on a cysteine-containing peptide.

Aebersold generally describes a method for quantitative analyses of proteins or protein function in mixtures of proteins. Aebersold does not teach or suggest blocking the free thiol groups with a blocking reagent, nor does Aebersold teach or suggest derivatizing the thiol group **after** enzyme digestion. In fact, Aebersold describes derivatizing the thiol groups **before** the digestion step, and hence teaches away from the present invention. Moreover, Aebersold does not teach or suggest reducing the disulfide bonds for a second time after the digestion step. Accordingly, Aebersold fails to teach or suggest every element of independent Claim 1. In addition, Aebersold does not teach or suggest a tagging reagent comprising a thiol-specific reactive group which is attached to a polymer tag via a linker. Therefore, Aebersold also fails to teach or suggest every element of independent Claim 16.

Huang does not cure the deficiency of Aebersold. With respect to independent Claim 1, Huang does not teach or suggest blocking the free thiol groups with a blocking reagent; nor does Huang teach or suggest derivatizing the thiol group after enzyme digestion; nor does Huang teach or suggest deprotecting the digested peptides to remove the blocking reagent.

With respect to independent Claim 16, Aebersold teaches derivatizing the thiol groups in a protein with a soluble affinity tag, digesting the tagged protein, and then separating the tagged peptides from untagged peptides by affinity isolation. This tag-before-digestion procedure precludes the possibility of using the tagging reagent of the present invention because the polymer tag of the present invention is insoluble and is better suited to a tag-after-digestion procedure. Therefore, Aebersold provides no desirability and thus the

obviousness of making the combination with Huang. Furthermore, the PEG copolymers of Huang contain a cysteamine-thiopyridine group that forms a disulfide bond with the cysteine-containing peptides. Therefore, even if one skilled in the art combines Aebersold with Huang, the final product may form a disulfide bond with the cysteine-containing peptide and is thus unusable for the present invention in which the tagging reaction is performed in the presence of a reducing agent. In other words, there is no reasonable expectation of success by simply combine the teachings of Aebersold and Huang. Accordingly, Applicants respectfully submit that Aebersold and Huang, individually or in combination, do not render independent Claims 1 and 16 obvious. Withdrawal of the 35 U.S.C. § 103 rejection to Claims 1 and 16 is respectfully requested.

If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed Cir. 1988). Accordingly, dependent Claims 2-4, 14-15, 17-19 and 21-23 are patentable because they depend from Claim 1 or Claim 16, and define additional patentable subject matter. Withdrawal of the 35 U.S.C. § 103 rejection to Claims 2-4, 14-15, 17-19, and 21-23 is respectfully requested.

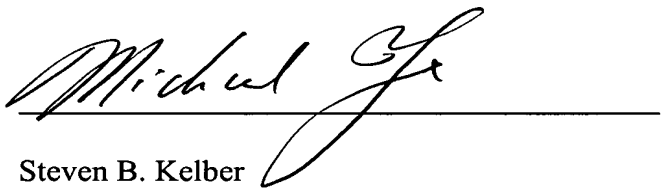
Allowable Claims

Applicants thank the Examiner for indicating that Claims 5-13 and 20 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. § 112, second paragraph, and to include all of the limitations of the base claim and any intervening claims. Claims 5-13 and 20 have been rewritten as new Claims 24-33. Allowance of new Claims 24-33 is earnestly solicited.

In view of the foregoing remarks, favorable reconsideration of all pending claims is requested. Applicants respectfully submit that this application is in condition for allowance and requests that a notice of allowance be issued. Should the Examiner believe that anything further is required to expedite the prosecution of this application or further clarify the issues, the Examiner is requested to contact Applicants' representative at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP



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